PATENT--FEE

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:

TIMOTHY J. MARTINS ET AL.

Continuation of Serial No. 09/731,591 filed December 7, 2000

Filed: Herewith

For: **CYCLIC AMP-SPECIFIC PHOSPHODIESTERASE INHIBITORS**

Group Art Unit: 1626

Examiner: E. Sackey

Attorney Docket No. 27866/38184

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Date of Deposit: **February 15, 2002**

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Richard Zimmermann

PRELIMINARY AMENDMENT ACCOMPANYING NEW APPLICATION TRANSMITTAL

Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified application filed under 37 C.F.R. §1.53(b) as follows:

IN THE SPECIFICATION:

Page 1, after the title, delete the CROSS REFERENCE TO RELATED APPLICATIONS in its entirety, and insert the following Cross-Reference to Related Applications:

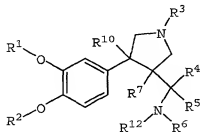
--CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Serial No. 09/731,591, filed December 7, 2000, now U.S. Patent No. _____, which claims the benefit of provisional application Serial No. 60/171,023, filed December 23, 1999.--

IN THE CLAIMS:

Cancel claims 1-45.
Add new claims 46-51:

--46. A method of inhibiting IL-1β release by monocytes in a mammal comprising administering to said mammal a therapeutically effective amount of a compound having a formula:



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearylO-aryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$, $C(=O)R^7$, $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl, C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, $C(=O)C_{1-3}$alkyleneC(=O)OR^7, C_{1-3}alkylene-heteroaryl, C(=O)C(=O)OR^7, $C(=O)C_{1-3}$alkyleneC(=O)OR^7, $C(=O)C_{1-3}$alkyleneNH(C=O)OR^7, $C(=O)C_{1-3}$alkyleneNH$_2$, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cycloalkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or $C(=O)R^7$;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a heterocycle, aralkyl, and aryl, and R^7 can be optionally substituted with one or more of RO^8, NR^8R^9, or SR^8;

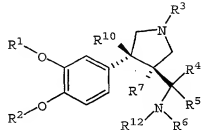
R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, heteroalkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)-Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9;

salts and solvates thereof.

47. The method of claim 46 wherein the compound has the structure:



48. The method of claim 46 wherein the compound is selected from the group consisting of

Methyl (4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[benzylamino]methyl}pyrrolidine carboxylate

Methyl (4S,3R)-3-(aminomethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[methylsulfonyl)amino]methyo}pyrrolidinecarboxylate

Methyl (4S,3R)-3-[(acetylamino)methyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl (4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-[(phenylcarbonylamino)methyl]pyrrolidinecarboxylate

Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[phenylsulfonyl)amino]methyl}pyrrolidinecarboxylate

Bis{[(4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-carboxymethylpyrrolidin-3-yl]methyl}amine

1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethylamine

1-{(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethylamine

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}benzamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}benzamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}acetamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}acetamide

3-(S)-(1-Acetylaminoethyl)-4-(S)-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(phenylsulfonyl)-amine

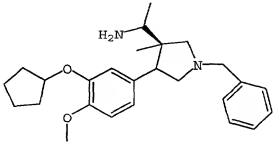
{1-[(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(phenylsufonyl)amine

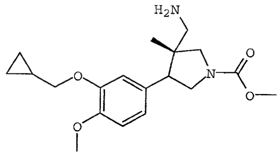
{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(methylsulfonyl)-amine

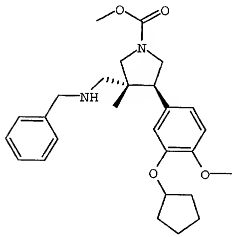
{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(methylsulfonyl)-amine, and

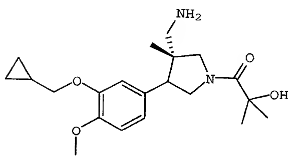
Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-[(methylamino)ethylpyrrolidine carboxylate.

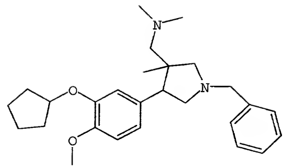
49. The method of claim 46 wherein the compound is the group consisting of:

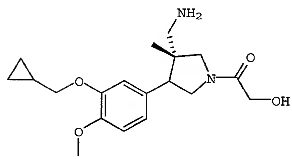


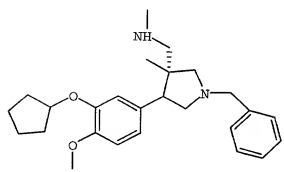


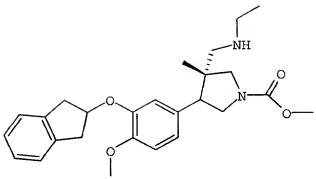




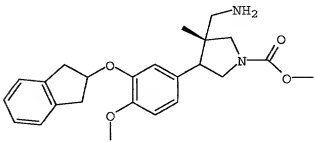




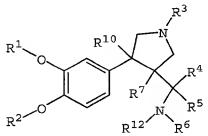




and



50. A method of inhibiting activation of human T-lymphocytes in a mammal comprising administering to said mammal a therapeutically effective amount of a compound having a formula:



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearyl-Oaryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$, $C(=O)R^7$, $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl, C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C_{1-3}alkylene-heteroaryl, C(=O)C(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneNH(C=O)OR^7, C(=O)C_{1-3}alkyleneNH_2, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cycloalkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or C(=O)R^7;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a heterocycle, aralkyl, and aryl, and R^7 can be optionally substituted with one or more of RO^8, NR^8R^9, or SR^8;

R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, hetero-

alkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

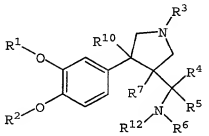
R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9;

salts and solvates thereof.

51. A pharmaceutical composition comprising

(a) a compound having a formula



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearylOaryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of C(=O)OR^7, C(=O)R^7, C(=NH)NR^8R^9, C(=O)NR^8R^9, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl,

C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C_{1-3}alkyleneheteroaryl, C(=O)C(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneNH(C=O)OR^7, C(=O)C_{1-3}alkyleneNH$_2$, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cycloalkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or C(=O)R^7;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a heterocycle, aralkyl, and aryl, and R^7 can be optionally substituted with one or more of RO^8, NR^8R^9, or SR^8;

R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, heteroalkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9,

and salts and solvates thereof;

(b) a pharmaceutically acceptable carrier; and

(c) a second therapeutic agent having utility in the treatment of rheumatoid arthritis.--

REMARKS

Claims 1-45 are pending in the application. Claims 1-45 have been cancelled, and new claims 46-51 have been added to the application by this amendment. Therefore, claims 46-51 are at issue in this continuation application.

This preliminary amendment adds no new matter. The specification has been amended to insert a cross-reference to a related application. Claims 46-51 are fully supported in the specification, for example, at page 4, lines 10-15 and 26-28, at page 40, lines 14-31, and in the originally filed claims, for example, claims 1, 2, 12, and 13.

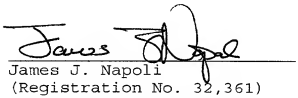
Pursuant to 37 C.F.R. §1.121, a marked-up version of the changes made to the claims by the present amendment is attached hereto following the signature page of this amendment. The first page of the marked-up version of the changes is captioned "Version With Markings to Show Changes Made."

It is submitted that the claims are in proper form and scope for allowance. Early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN

By 

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Chicago, Illinois
February 15, 2002

Version with Markings to Show Changes Made
Continuation of U.S.S.N. 09/731,591
(27866/36007A), filed December 7, 2000

IN THE SPECIFICATION:

A new cross-reference to related application has been added to the specification at page 1, after the title, as follows:

--CROSS-REFERENCE TO RELATED APPLICATIONS

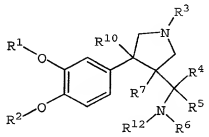
This application is a continuation of application Serial No. 09/731,591, filed December 7, 2000, now U.S. Patent No. _____, which claims the benefit of provisional application Serial No. 60/171,023, filed December 23, 1999.--

IN THE CLAIMS:

Cancel claims 1-45.

New claims 46-51 have been added as follows:

46. A method of inhibiting IL-1β release by monocytes in a mammal comprising administering to said mammal a therapeutically effective amount of a compound having a formula:



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearylO-aryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$, $C(=O)R^7$, $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl, C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C_{1-3}alkylene-heteroaryl, C(=O)C(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneNH(C=O)OR^7, C(=O)C_{1-3}alkyleneNH_2, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cyclo-alkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or $C(=O)R^7$;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a hetero-cycle, aralkyl, and aryl, and R^7 can be optionally substi-tuted with one or more of RO^8, NR^8R^9, or SR^8;

R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cyclo-alkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, hetero-

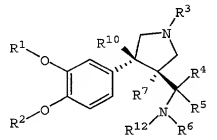
alkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)-Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9;

salts and solvates thereof.

47. The method of claim 46 wherein the compound has the structure:



48. The method of claim 46 wherein the compound is selected from the group consisting of

Methyl (4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[benzylamino]methyl]}pyrrolidine carboxylate

Methyl (4S,3R)-3-(aminomethyl)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[methylsulfonyl)amino]methyo}pyrrolidinecarboxylate

Methyl (4S,3R)-3-[(acetylamino)methyl]-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidinecarboxylate

Methyl (4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-[(phenylcarbonylamino)methyl]pyrrolidinecarboxylate

Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-{[phenylsulfonyl)amino]methyl}pyrrolidinecarboxylate

Bis{[(4S,3R)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-carboxymethylpyrrolidin-3-yl]methyl}amine

1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethylamine

1-{(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethylamine

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}benzamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}benzamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}acetamide

N-{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}acetamide

3-(S)-(1-Acetylaminoethyl)-4-(S)-(3-cyclopentyloxy-4-methoxyphenyl)-3-methylpyrrolidine-1-carboxylic acid methyl ester

{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(phenylsulfonyl)-amine

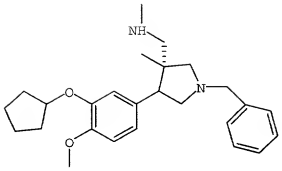
{1-[(3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(phenylsufonyl)amine

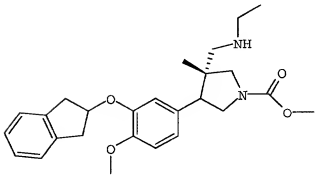
{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(methylsulfonyl)-amine

{1-[(3S,4S)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-methyl-1-benzylpyrrolidin-3-yl]ethyl}(methylsulfonyl)-amine, and

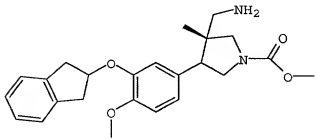
Methyl (3S,4S)-4-(3-cyclopentyloxy-4-methoxyphenyl)-3-methyl-3-[(methylamino)ethylpyrrolidine carboxylate.

49. The method of claim 46 wherein the compound is the group consisting of:



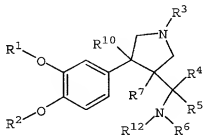


and



50. A method of inhibiting activation of human T-lymphocytes in a mammal comprising administering to

said mammal a therapeutically effective amount of a compound having a formula:



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearyl-Oaryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$, $C(=O)R^7$, $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl, C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C_{1-3}alkylene-heteroaryl, C(=O)C(=O)OR^7, C(=O)C_{1-3}alkyleneC(=O)OR^7, C(=O)C_{1-3}alkyleneNH(C=O)OR^7, C(=O)C_{1-3}alkyleneNH$_2$, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cycloalkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or $C(=O)R^7$;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a heterocycle, aralkyl, and aryl, and R^7 can be optionally substituted with one or more of RO^8, NR^8R^9, or SR^8;

R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, heteroalkaryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

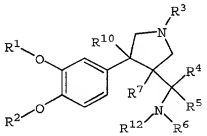
R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9;

salts and solvates thereof.

51. A pharmaceutical composition comprising

(a) a compound having a formula



wherein R^1 is lower alkyl, bridged alkyl, aryl, heteroaryl, aralkyl, cycloalkyl, a 5- or 6-membered saturated heterocycle, C_{1-4}alkylenearyl, C_{1-4}alkyleneOaryl, C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneHet, C_{2-4}alkylenearylOaryl, C_{1-4}alkylene bridged alkyl, C_{1-3}alkylenecycloalkyl, substituted or unsubstituted propargyl, substituted or unsubstituted allyl, or halocycloalkyl;

R^2 is hydrogen, methyl, or halo-substituted methyl;

R^3 is selected from the group consisting of $C(=O)OR^7$, $C(=O)R^7$, $C(=NH)NR^8R^9$, $C(=O)NR^8R^9$, lower alkyl, bridged alkyl, cycloalkyl, haloalkyl, halocycloalkyl, C_{1-3}alkylenecycloalkyl, a 5- or 6-membered saturated heterocycle, aryl, heteroaryl, C_{1-3}alkyleneC(=O)R^7, C(=O)-C(=O)NR^8R^9, C_{1-4}alkyleneOR^7, C_{1-3}alkylenearyl, SO_2heteroaryl, Het, aralkyl, alkaryl, heteroaralkyl, heteroalkaryl, C_{1-3}alkyleneC(=O)OR^7, $C(=O)C_{1-3}$alkyleneC(=O)OR^7, C_{1-3}alkyleneheteroaryl, $C(=O)C(=O)OR^7$, $C(=O)C_{1-3}$alkyleneC(=O)OR^7, $C(=O)C_{1-3}$alkyleneNH(C=O)OR^7, $C(=O)C_{1-3}$alkyleneNH$_2$, and NHC(=O)OR^7;

R^4 is hydrogen, lower alkyl, haloalkyl, cycloalkyl, or aryl;

R^5 is hydrogen, lower alkyl, alkynyl, haloalkyl, cycloalkyl, or aryl;

R^6 and R^{12}, independently, are hydrogen, lower alkyl, aralkyl, SO_2R^{11}, or $C(=O)R^7$;

R^7 is selected from the group consisting of branched or unbranched lower alkyl, heteroaryl, a heterocycle, aralkyl, and aryl, and R^7 can be optionally substituted with one or more of RO^8, NR^8R^9, or SR^8;

R^8 and R^9, same or different, are selected from the group consisting of hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, alkaryl, heteroaralkyl, heteroalk-

aryl, and aralkyl, or R^8 and R^9 can be taken together form a 4-membered to 7-membered ring;

R^{10} is hydrogen, alkyl, haloalkyl, cycloalkyl, aryl, C(=O)alkyl, C(=O)cycloalkyl, C(=O)aryl, C(=O)Oalkyl, C(=O)Ocycloalkyl, C(=O)aryl, CH_2OH, CH_2Oalkyl, CHO, CN, NO_2, or SO_2R^{11};

R^{11} is alkyl, cycloalkyl, trifluoromethyl, aryl, aralkyl, or NR^8R^9,

and salts and solvates thereof;

(b) a pharmaceutically acceptable carrier; and

(c) a second therapeutic agent having utility in the treatment of rheumatoid arthritis.